IPEC Americas –FDA-OGD Meeting, Inactive Ingredient Database (IID)

December 7, 2012

FDA Center in Rockville

Meeting Attendees

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Meeting Purpose

This meeting was the fourth of several meetings between IPEC Americas and the FDA OGD team identified to help resolve current issues with the FDA IID which have ultimately impacted abbreviated new drug applications (ANDAs). This team was created based on IID concerns identified at a joint meeting between IPEC Americas members and FDA OGD personnel on December 9th, 2011. Minutes from previous meetings are located at:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm142112.htm

Meeting Agenda and Actions

1. Introductions

Brief introductions and review of meeting agenda.

2. Review of Status of FDA's Approval of the Hypromellose and Polyethylene Oxide Spreadsheets and Timeline for Posting on OGD Website

FDA-OGD has received approximately 1100 new ANDA applications in 2012, of which only a portion are identified as being a part of the backlog (those ANDAs received on Jan 1 2012 to Sept 30, 2012). Currently there are approximately 2900 ANDA application in the backlog.

OGD and IPEC have selected several excipients to review with regards to the effects of the grade, viscosity, and so forth on drug product safety.

Jim Osterhout is in charge of the safety review and is currently reviewing the information for hypromellose. In his preliminary findings, the excipient grade listed in the spreadsheet appear to be essentially the same. This finding will allow the OGD and IPEC to continue talks to determine if “familial ties” will apply to these excipients and thus will eliminate the request for additional pharm/tox data to be submitted at time of filing or during the technical review process. Further review will be required for new routes of delivery or different product forms, as these reviews are centered around the oral route of administration. Use of large amounts of HPMC in an oral product may also become a review issue if the amount of HPMC is expected to cause a clinical effect. (i.e. laxative effect) even if the levels are considered safe.

The FDA expressed their agreement that the quality of the summaries provided were excellent and encouraged industry to continue to maintain and/or improve the quality of future submissions.

The FDA is targeting Q1, 2013 to finish their update to the spreadsheet for HPMC; however, with limited resources, this would be the earliest release. The review of polyethylene oxide should be less difficult and the spreadsheet may also be completed/posted by mid-2013.

Once the spreadsheet is approved, the FDA plans to post information in a similar method as currently utilized for Patent Certifications. [1]

ACTION 1: FDA to post updated hypromellose data once the full review is completed. Jim is currently targeting posting the updated table information in Q1, 2013.

IPEC Americas members requested the FDA include some text on how they plan to use the information in the table. It was also proposed the reference document could potentially include a listing for pending and future material for review by FDA. IPEC will then post information about the table and use of the table via various area IPEC websites and general newsletters (e.g. IPEC Americas Insider).

ACTION 2: FDA to mimic Paragraph 4 web-page, including introductory information on what/how to use the reviewed excipient IID tables along with a direct link to a PDF document that contains information from the spreadsheet.

ACTION 3: IPEC America's members to post information about the table(s) and use of information from the tables using various IPEC websites and newsletters.

Based on discussion during the meeting, the FDA noted use of the tables, information contained in the tables and other related IID discussions/upgrades will be communicated to FDA reviewers as part of their 2013 training. IPEC Americas members have offered to provide assistance with training.

ACTION 4: FDA/OGD to host training for their reviewers in order to demonstrate how to utilize the spreadsheet information for materials listed, rather than relying on the IID database for these particular inactives. If acceptable, the OGD will ask IPEC members to aid with training.

In addition, FDA will consider communicating information on IID upgrades and use of the spreadsheets at a GPhA-FDA CMC workshop in May 2013.

Based on the GDUFA plan, the FDA will be authorized to hire and train additional personnel to perform ANDA reviews in the new hire's field(s) of expertise. This will allow OGD to streamline and prioritize its review process so it can meet GDUFA goals. A portion of GDUFA allows for additional IT resources, which may include future work to improve/develop the next generation of a more user-friendly IID.

Using the same formats (spreadsheet and toxicology assessment) as previously developed for hypromellose and polyethylene oxide reviews, issues with two new classes of materials (silicones and carbomers) were discussed during the December 7th, 2012 meeting.

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[1] FDA Paragraph IV Patent Certifications
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm047676.htm

3. Spreadsheet and supporting safety information for Silicone Family of products

Silicone products are sold in various forms (volatile fluids, non-volatile fluids, emulsions, elastomers, pressure sensitive adhesives, etc) and have been used in approved drug products for more than 40 years (first DMF submitted in 1954).

For this meeting, a spreadsheet of listings for various forms of silicone was prepared and discussed. Toxicology summaries were prepared and shared for: cyclomethicones, dimethicones, simethicones/simethicone emulsions and silicone pressure sensitive adhesives. Although proposed maximum dose levels were included in the meeting discussions (based on maximum precedence dose levels and toxicology studies), the main emphasis for discussion pertained to issues with "nomenclature." Many of these concerns were summarized below:

- CYCLOMETHICONE: Current listings for "Cyclomethicone" are generic (both in ingredient nomenclature and UNII code assignment) and do not differentiate between single cyclomethicone ingredients (such as D4, D5 or D6) and mixtures thereof. Current UNII code assignments have already been established for each cyclic ingredient (D4, D5 and D6) and were included in the table. Based on differences in toxicological profiles for individual ingredients (especially between D4 and D5/D6) FDA reviewers might want to be more specific for future listings. A toxicology summary document was provided along with a reference to where complete study reports could be found (see Dow Corning DMF reference in Column J).
- DIMETHICONE: current listings for dimethicone include a "number" which could either refer to a TRADE name designation (e.g. 360 most likely refers to DOW CORNING® 360 Medical Grade Fluid) or to a median viscosity (e.g. 350 and 1000 most likely refer to 350 cSt and 1000 cSt, respectively). Although the current database does not include specific references to other viscosities (e.g. 20 cSt, 100 cSt, 500 cSt, 12500 cSt), drug products have been produced with fluids over the entire range of viscosities (not just 350 cSt and 1000 cSt). A toxicology summary covering a range of viscosities for dimethicone fluids was provided to the FDA. In addition, UNII listings for each dimethicone viscosity and a Dow Corning DMF reference for location of complete toxicology study reports (Colum J) were provided in the spreadsheet.
- DIMETHICONE COPOLYOL: Based on assigned UNII codes for at least 5 different dimethicone copolyols (see spreadsheet), it is not clear with dimethicone copolyol has been approved and listed in the current IID. It would be useful to either create a "generic" UNII code that would cover the range, or better define in the IID which one(s) have been used in approved products.
- DIMETHYLSOLOXANE/METHYLVINYSILOXANE COPOLYMERS: there are currently several listings for "cured silicone rubbers/elastomers" which either include reference to a TRADE name (MDX4-4210) or "one" of the ingredients used to produce the cured article (vinyl siloxane). Cured article listed in the IID are actually produced from a mixture of a copolymers containing "≡SiCH=CH_2" and "≡SiH" functionality and would be better designated as: dimethicone/vinylmethicone **crosspolymers**. Although no specific toxicology summary was provided for this class of materials, references to several Dow Corning DMFs which contain full toxicology study reports were provided in Column J.
- POLYSILOXANE, SILICON DIOXIDE, SILICONE and SILICON: The current IID includes several "generic" listings for a very broad family of materials. Based on the current ingredient nomenclature, almost any "silicone/silicon" containing product could reference these listings. Since "silicon" is an element (see picture below), it is HIGHLY UNLIKELY that this ingredient is actually used in a drug product. It is highly recommended that FDA work to clean-up the current version of the IID by replacing these generic listings with more definitive nomenclature for the actual

ingredient used. K. Ulman offered to help with re-naming these materials if provided with more information on the type of silicone ingredient used.

- SILICONE ADHESIVES: Currently the IID nomenclature used for silicone pressure sensitive adhesives used in approved drug products (mostly transdermal) vary widely (some include part of a TRADE name (MDX4-4036, 4102, 4502, S-15) and others include reference to a film strip containing silicone. Recently, working with Larry Callahan, UNII codes were assigned based on both adhesive functionality and resin/polymer compositions. Robert Iser was given a PROPRIETARY table of information which included reference to several commercial transdermal products (including NDA/ANDA numbers) containing silicone adhesives, along with their UNII code assignments. Since it is currently very difficult for drug manufacturers to identify current IID listings with the various silicone adhesives used in approved TDDS products, it would be extremely helpful if the FDA could update the nomenclature and UNII codes based on the table of commercial product information provided. In addition, a toxicology summary was provided that showed the safety for the family of adhesive materials. A reference to Dow Corning DMFs containing the full toxicology study reports was also provided (Column J).
- SILICONE EMULSIONS, SIMETHICONES and SIMETHICONE EMULSIONS: it was noted that although the nomenclature for these products defines the "generic" polymer and/or composition of these materials, the current naming does not specify the "viscosity" of the dimethicone fluid used or (for the simethicone and/or simethicone emulsion) the type of silica used (fumed, amorphous, precipitated, etc). A toxicology summary was provided covering different formulations for these materials produced by Dow Corning (including DMF references to full toxicology study reports, Column J), but study results may not be applicable to all silicone emulsions, simethicones or simethicone emulsions produced by other vendors.

ACTION 5: Based on 36+ years as a chemist working with silicones, K. Ulman offered to provide further silicone chemistry/nomenclature support to clean-up nomenclature issues for silicone materials listed in the IID.

4. Spreadsheet for Carbomer Family of products

The second class of materials discussed at the December 2012 meeting included carbomers.

Carbomers were introduced 50 years ago and have been in global commercial use in many industries, including use as pharmaceutical excipients. Established pharmaceutical uses range from rheology modifiers for topical and liquid products to applications in oral solid dose products (tablets and capsules) as binders and modified-release agents. FDA has approved products containing these carbomer polymers for over 30 years.

These products are commonly known by several different generic names including carboxypolymethylene, carbomer, etc. The current IID nomenclature includes references to various TRADE and compendial names.

Carbomers were traditionally manufactured in benzene, and over time have evolved to products polymerized in more toxicologically preferred solvents (e.g. ethyl acetate, cyclohexane). Meera Raghuram noted that she has worked with personnel at the FDA (Drs. Larry Callahan and Frank Switzer) and that updated UNII codes have been assigned based on composition and grades of carbomers. A spreadsheet of IID listings for carbomers was presented along with the following description for the information included in each column of the spreadsheet:

1. Column A – Inactive Ingredient:

- Carbomer is the most widely known generic term used to describe cross-linked polyacrylic acid products as a class. Other names currently used in the Inactive Ingredients Database are "carboxypolymethylene," "carbomer homopolymer," and "carbomer," in addition to compendial names.
- "Traditional" carbomer polymers initially included in the U.S. Pharmacopeia/National Formulary (USP/NF) were polymerized in benzene solvent; however, over time new carbomers were produced in more toxicologically preferred solvents (e.g. ethyl acetate or a cosolvent mixture of ethyl acetate and cyclohexane).
- Initially, USP allowed carbomer polymers produced either in benzene or more toxicologically preferred solvent products to utilize the same generic compendial name; therefore, a trade name change was required without changing the compendial name. The nomenclature difference between the compendial and product trade name has been a source of confusion because the NF Carbomer designation has historically applied to more than one Carbopol® product where chemical similarities exist.
- In order to minimize confusion, umbrella monographs have been developed to separate Carbomer products that are manufactured without the use of benzene as a polymerization solvent. The Carbomer Homopolymer monograph became effective in USP 29-NF 24 in January 2006, with a delayed a delayed implementation date up to January 1, 2011

2. Column B – Synonym:
   - The synonym field contains potential synonyms for inactive ingredients listed in column A including generic names and trade names.
3. Columns- C (Route), D (Dosage Form), E (CAS #), F (UNII), G (Maximum Potency), H (Unit):
   - This includes information from the IID database. It was pointed out that the UNII codes have been updated by FDA based on chemistry and supporting information provided by Lubrizol.
4. Column I – Based on safety data for family of related products, maximum precedence of use level for route:
   - This column contains a Maximum Precedence of Use level, for a specific route of administration, based on safety data for the carbomer family of related products.
   - The proposed maximum precedence of use level for sustained release oral tablets (line 2) currently in the IID is 195 mg of carboxypolymethylene.
   - The proposed maximum precedence of use level for topical application (line 18) currently in the IID is 3.5% of carbomer 940.
5. Column J – Maximum Daily Intake Precedence of use based on Safety Data – No information is currently available.
6. Colum K – Maximum Allowable Concentration based on Existing Safety Data – A report titled "Toxicology and Regulatory Review" was provided to FDA. This document summarizes the Lubrizol safety data and contains bridging arguments for the chemical and toxicological equivalence of the carbomer homopolymer family of excipients. The acceptable daily dose, calculated from available toxicology data, demonstrates that consumption of carbomer homopolymers (manufactured in ethyl acetate as solvent) should be safe if 3,553 mg per day or less is ingested in a pharmaceutical product.
7. Column I – Lubrizol is going to establish a Type V DMF with bridging arguments and safety studies so information is available in one place.

Based on information provided above, a family approach was recommended for listing carbomers in the IID. It was further noted that carbomers A, B and C are interchangeable except for viscosity. To support this, a confidential copy of bridging data based on historical toxicological studies/data was provided to FDA/OGD personnel. From these studies, proposed IID levels were suggested based on the non-benzene produced materials. Full toxicology study reports will be submitted in a Type V DMF.

Also, it was noted there are known higher levels of carbomer used in approved drug products that are not currently included in the IID. Is there a way to submit information to someone at the FDA which would allow for an update of listings? If so, what type of information would need to be submitted, and to whom?

5. Draft IID Q&A Document for OGD Posting - Including Proposed Answers and Meeting Notes

A DRAFT copy of an IID Q&A, which included proposed responses extracted from previous FDA/OGD-IPEC Americas working meeting minutes and from IPEC Americas members, was shared with the FDA/OGD Excipient working group. Due to time limitations, it was not possible to discuss all of the proposed responses during the meeting; however, IPEC Americas members identified five (5) questions, as listed below. They requested further clarification on:

Q7 Meeting Note: Ask the FDA to clarify if toxicity data should only be provided in a Type V DMF and if the Type IV DMF should only include CMC information.

Q10 Meeting note: Can FDA provide a typical time frame for an average toxicology consultation?

Q17 Meeting Note: Will FDA consider adding inactive ingredients used in OTC monographs and not used in an approved NDA/ANDA drug product?

Q18 Meeting Note: Meeting Note: If industry knows of an excipient used in approved drug products or at higher levels than currently listed in the IID, can an expedited mechanism be used to include these in the IID?

Q29 Meeting Note: For multi-strength dosages, what is FDA's position on how excipient levels are calculated to determine daily dose?

Lisa noted this question was timely because the FDA is currently working on how to handle this. IPEC members suggested that it would be helpful to have rules created and documented.

Due to limited time to discuss the proposed answers or the special "meeting notes" for each of the questions, it was agreed the team would review the Q & A document at the team's next meeting.

ACTION 6: FDA-OGD/IPEC Americas working team to review DRAFT Q&A document during next meeting.

6. Select Next Meeting Dates for 2013

FDA will get back to us whether March 1st 2013 will work for them as next meeting date. IPEC should send their questions and requests to Lisa Tan prior to the next meeting for consideration.